Annual Reporting Form for SCEDDBO Projects and Cores

Research Project A: Mapping Disparities in Birth Outcomes

Period covered by the report: 5/1/2011 – 4/30/2012
EPA Agreement Number: RD83329301-0
Investigators: Marie Lynn Miranda (PI), Alan Gelfand, Pamela Maxson, Evan Myers
Project Period: Year 5
The central objective of Project A is to determine whether and to what extent joint exposures to socioeconomic and environmental stressors contribute to racial and ethnic health disparities in fetal growth restriction. Using a geographically-based nested study design moving from analysis of births for the entire State of North Carolina to six demographically and geographically distinct counties to a single health center and state-of-the-art Geographic Information Systems applications with Bayesian spatial hierarchical modeling and other advanced spatial statistical approaches, the specific aims are to:

1. Spatially link detailed birth record, fetal death certificates, socioeconomic, environmental, tax assessor, community-based, and clinical obstetric data at highly resolved scales for the State of North Carolina from 1990-2003;
2. Refine the concept of fetal growth restriction by a) developing a joint distribution for birthweight and gestation using bivariate modeling for live births and fetal deaths – both separately and jointly, and b) defining it in terms of fetal and infant mortality, rather than percentile cut points; and
3. Determine whether and to what extent differential exposures to both environmental and social stressors help explain health disparities in fetal growth restriction among a) African-American women compared to Non-Hispanic white and Hispanic women, b) Older African-American women compared to younger African-American women, c) Hispanic women compared to Non-Hispanic white and African-American women, and d) Foreign born Hispanic women compared to US born Hispanic women.

Summary of Accomplishments

A continuing goal is the linking of the detailed birth record data to USEPA PM_{10}, $PM_{2.5}$, and ozone monitoring data in order to study the impact of *maternal exposure to air pollution* on birth weight. We are especially focused on refining exposure metrics to most effectively characterize meaningful exposures, as well as to capture any windows of vulnerability. Significant progress has been made on the relationship between birth outcomes and exposure to particulate matter and ozone separately, and the current focus is determining how to characterize joint exposure to both particulate matter and ozone.

Ongoing work has been devoted to a novel project concerned with connecting the *built environment* to adverse pregnancy outcomes. Built environment data has been collected under the Community Assessment Project and, after preliminary analysis has focused on spatial layers capturing four primary attributes of the built environment: housing damage, property disorder, tenure, and vacancy. Connection has been made to preterm birth and low birth weight.

Our work on *racial residential segregation* can be connected to measures of social and economic disadvantage at these scales to gain insight into how racial residential segregation has manifested itself across urban landscapes. In turn, this promises to reveal key insights into how to think about the spatial aspects of the social factors influencing health disparities. We are

working to determine which facets of segregation best characterize the way community-level racial residential segregation acts to promote health disparities in birth outcomes, as well as how those facets correlate with environmental exposures and disamenities.

We continue to work on developing methods to look at environmental exposures and pregnancy outcomes. We are building *spatial downscalers*, which enable the fusion of monitoring station data with computer model output to better assess environmental exposure at point level spatial resolution. We are also looking at *joint models for birthweight and gestational age* using bivariate normal mixtures. Such joint modeling adjusts for maternal risk factors and provides mixture analysis of the residuals to help illuminate further subpopulations with differential risk for adverse joint birth outcomes. In addition, we have examined quantile regression methodology in explaining the effect of exposure on pregnancy outcomes. Rather than explaining mean birthweight as in customary regression models, we are interested in explaining quantiles for birthweight. Our analysis indicates that risk factors and environmental exposures affect different quantiles differently. We have also completed considerable methodological work on expected performance accruing to *synthesizing categorical datasets* with the objective of enhancing inference. We are particularly interested in how to deal with a collection of datasets of varying sizes that are all relevant to a particular scientific question, but which include different subsets of the relevant variables, with some overlap.

Future Activities

We plan to continue working on each of the areas described in the progress report/summary of accomplishments section. Achieving a better understanding of exposure to air toxicants, particularly particulate matter and ozone, is a central focus of our future efforts. We continue the process of linking participants in Project B with their associated birth certificate record. This linkage allows us to explore issues of data accuracy in the detailed birth record, as well as to begin implementing the methods of synthesizing categorical data.

Publications

Anthopolos, R., James, S.A., Gelfand, A.E., Miranda, M.L. 2011. “A Spatial Measure of Neighborhood-level Racial Isolation Applied to Low Birthweight, Preterm Birth, and Birthweight in North Carolina.” *Spatial and Spatio Temporal Epidemiology.* 2(4): 235-246. PMID: 22748223.

Berrocal, V., Gelfand, A., Holland, D. 2012. “Space-time Data Fusion under Error in Computer Model Output: an Application to Air Model Quality.” *Biometrics*. Forthcoming.

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Chang H.H., Reich B.J., and Miranda M.L. “A Spatial Time-to-Event Approach for Estimating Associations between Air Pollution and Preterm Birth.” *Journal of the Royal Statistical Society: Series C (Applied Statistics).* Forthcoming.

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Miranda, M.L., Edwards, S.E. 2011. “Use of Spatial Analysis to Support Environmental Health Research and Practice.” *North Carolina Medical Journal*. 72(2):132-135. PMID: 21721500.

Miranda ML, Edwards SE, Chang HH, Auten RL. “Proximity to Roadways and Pregnancy Outcomes.” *J. Exp Science Env Epi*. In press.

M.L. Miranda, S.E. Edwards, R. Anthopolos, D. H. Dolinsky, A. R. Kemper. 2012. "The Built Environment and Childhood Obesity in Durham, NC.” *Clinical Pediatrics*. 51 (8):746-754. PMID: 22563061.

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Miranda, M.L., Messer, L., Kroeger, G. 2012. “Associations between the Quality of the Residential Built Environment and Pregnancy Outcomes among Women in North Carolina." *Environmental Health Perspectives*. 120(3):471-477. PMCID: PMC3295337.

Montagna S, Tokdar ST, Neelon B, Dunson D. “Bayesian Latent Factor Regression for Functional and Longitudinal Data.” *Biometrics*. Forthcoming.

Neelon, B., Swamy, G.K., Burgette, L.F., Miranda, M.L. 2011. “A Bayesian Growth Mixture Model to Examine Maternal Hypertension and Birth Outcomes.” *Statistics in Medicine*. 30(22):2721-35. PMID: 21751226.

Vinikoor-Imler, L.C., Gray, S.C., Edwards, S. E., Miranda, M.L. 2012. "The Effects of Exposure to Particulate Matter and Neighborhood Deprivation on Gestational Hypertension." *Pediatric and Perinatal Epidemiology*. 26(2): 91-100. PMID: 22324494.

Supplemental Keywords

Data fusion, meta analysis, disparities, spatial disaggregation, spatial interpolation, spatial modeling, racial residential segregation

Research Project B: Healthy Pregnancy, Healthy Baby: Studying Racial Disparities in Birth Outcomes

Period covered by the report: 5/1/2010 – 4/30/2011
EPA Agreement Number: RD83329301-0
Investigators: Redford Williams (PI), Allison Ashley-Koch, Richard Auten, Pamela Maxson, Marie Lynn Miranda, Jerome Reiter, Geeta K. Swamy
Project Period: Year 5

The central objective of the Healthy Pregnancy, Healthy Baby Study is to determine how the interaction of environmental, social, and host factors contributes to disparities in birth outcomes between African-American and white women in the American South. There are four specific aims:

1. Conduct a cohort study of pregnant women in Durham, NC designed to correlate birth weight, gestation, and birth weight x gestation with environmental, social, and host factors;
2. Develop community-level measures of environmental and social factors by inventorying neighborhood quality and the built environment in partnership with local community groups;
3. Create a comprehensive data architecture, spatially resolved at the tax parcel level, of environmental, social, and host factors affecting pregnant women by linking data from the cohort study and neighborhood assessments with additional environmental and socioeconomic data; and
4. Determine whether and to what extent differential exposures explain health disparities in birth outcomes by applying innovative spatial and genetic statistical methods to:
    a. Identify environmental, social, and host factors that cluster to predict birth outcomes in the entire sample,
    b. Determine whether these clusters are more or less present in African-American versus white populations and quantify the proportion of health disparities explained by differences in cluster frequency, and
    c. Identify environmental, social, and host factors that cluster to predict birth outcomes within the African-American and white sub-samples and compare these clusters across racial groups.

Summary of Accomplishments

As of 4/1/2012, 1889 women have been enrolled in the study. Women are recruited from Duke University Medical Center (DUMC) and Lincoln Community Health Center. Demographic data indicate that we are successfully recruiting women who are most at risk for adverse pregnancy outcomes, particularly low-income, low educational attainment, and non-Hispanic black women. Data collection is now complete.

All maternal data are georeferenced (i.e., linked to the physical address of the mother) using Esri software. The Healthy Pregnancy/Healthy Baby Study also includes an in-depth neighborhood assessment designed to capture both built environment and community-level social stressors and community resources. The cohort study and neighborhood assessment data are spatially linked to extensive environmental and demographic data at a highly resolved spatial scale.

Genetic Data and Analysis. This project focused on genetic analysis of candidate genes, specifically those involving human environmental contaminant clearance (heavy metals and environmental tobacco smoke), infection and inflammation (cytokines, chemokines, and bacterial pathogen recognition), maternal stress response (serotonin), and other pathways that

have been implicated as potential drivers of health disparities (vascular responsivity). To date, we have genotyped 412 Single Nucleotide Polymorphisms (SNPs) in fifty-two candidate genes. This past year, we focused on completing the genotyping of those SNPs in the samples which had been most recently ascertained.

Psychosocial Indicators. Analyses have been completed on psychosocial influences on birth outcomes. In order to reduce the number of psychosocial variables, cluster analysis has been performed, resulting in three distinct clusters of women. A paper examining the relationship between the built environment as measured through the Community Assessment Project and women's psychosocial health was published in year 5. Future analyses will continue with a focus on the relationships among psychosocial health, risk behaviors, chemical and non-chemical stressors, and pregnancy outcomes.

Maternal Medical Complications. Fetal health is not only individually determined, but is also influenced by maternal health and well-being. This past year, we put additional emphasis on maternal outcomes.

Statistical Methods Development. We developed several new statistical methodologies designed to improve analysis of the Project B data, as well as to advance statistical analysis more broadly. First, we developed and implemented methods for finding important predictors in quantile regression when there are a very large number of covariates. These methods adapted the lasso and elastic net penalties for quantile regression. We applied the methods on a mid-study sample of women to uncover a previously unreported interaction: women who smoke and who have high blood lead levels tend to have babies with lower birth weights. Second, we developed and implemented methods for using factor analysis models in the context of quantile regression. The investigative team believes that many of the predictors can be grouped into underlying factors. Third, we developed and implemented methods for accounting for mid-study changes in measurement scales. These methods were needed because the Project B investigators switched laboratories for measuring blood levels of heavy metals midway through data collection in order to take advantage of finer measurement scales. Exploratory analysis indicated that the distributions of levels for several exposures were markedly different across the labs, so that analyses based on a simple concatenation of the two labs' data would be biased. We also developed a Bayesian growth mixture model to jointly examine the associations between longitudinal blood pressure measurements, preterm birth (PTB), and low birthweight (LBW). The model partitions women into distinct classes characterized by a mean arterial pressure (MAP) curve and joint probabilities of PTB and LBW. Each class contains a unique mixed effects model for MAP with class-specific regression coefficients and random effect covariances. To account for the high correlation between PTB and LBW, we introduce a bivariate probit model within each class to capture residual within-class dependence between PTB and LBW. The model permits the association between PTB and LBW to vary by class, so that for some classes, PTB and LBW may be positively correlated, while for others, they may be uncorrelated or negatively correlated.

We also focused statistical methods development on the genetic data. The first statistical innovation involving the genetic data is the adverse sub-population regression (ASPR) for multivariate outcomes with high dimensional predictors. The ASPR is a two component latent class model, with the dominant component corresponding to (presumed) healthy individuals and the risk of falling in the minority component characterized via a logistic regression. The logistic regression model is designed to accommodate high-dimensional predictors, as occur in studies with a large number of gene by environment interactions, through use of a flexible

nonparametric multiple shrinkage approach. The Gibbs sampler is developed for posterior computation.

Future Activities

In the next year, we will focus on data analysis and further statistical methods innovation. Our overall goal is to identify complex interactions among host, social, and environmental contributors. With the data collection complete, we will are well-positioned to examine and identify combinations of factors that lead to health disparities in birth outcomes. We are particularly interested in identifying chemical and non-chemical environmental risk factors given that they are actionable to improve birth outcomes.

Publications

Burgette LF, Reiter JP, Miranda ML. 2011. "Exploratory Quantile Regression with Many Covariates: an Application to Adverse Birth Outcomes." *Epidemiology*. Nov;22(6):859-66.

Burgette LF, Reiter JP. 2012. "Modeling Adverse Birth Outcomes via Confirmatory Factor Quantile Regression." *Biometrics*. Mar;68(1):92-100.

Burgette LF, Reiter JP. 2012. "Nonparametric Bayesian Multiple Imputation for Missing Data due to Mid-study Switching of Measurement Methods." *Journal of the American Statistical Association.*

Buttke DE, Wolkin A, Stapleton HM, Miranda ML. 2012. "Associations between Serum Levels of Polybrominated Diphenyl Ether (PBDE) Flame Retardants and Environmental and Behavioral Factors in Pregnant Women." *J.Expo.Sci.Environ.Epidemiol*.

Chang HH, Reich BJ, Miranda ML. 2012. "Time-to-Event analysis of Fine Particle Air Pollution and Preterm Birth: Results from North Carolina, 2001-2005." *Am.J.Epidemiol*. 15;175(2):91-8.

Chang HH, Reich BJ, Miranda ML. 2012. "Response to Dr. Zeger: Epidemiologic Studies of the Health Associations of Environmental Exposures with Preterm Birth." *American Journal of Epidemiology*. 15:175(2): 111-112.

Chang HH, Reich BJ, and Miranda ML "Spatial Time-to-Event Analysis of Air Pollution and Preterm Birth." *Journal of the Royal Statistical Society Series C*. Forthcoming,

Maxson PJ, Edwards SE, Ingram A, Miranda ML. 2012. "Psychosocial Differences between Smokers and Nonsmokers during Pregnancy." Addict.Behav. 37(2):153-9.

Maxson P, Miranda ML. 2011. "Pregnancy Intention, Demographic Differences, and Psychosocial Health.".*J.Womens Health.* 20(8):1215-23.

Messer LC, Miranda ML, Maxson P. The Built Environment and Women's Psychosocial Health. *Journal of Urban Health*. Forthcoming.

Miranda, M.L., Edwards S., Chang, H., Auten, R. Proximity to Roadways and Pregnancy Outcomes. *Journal of Exposure Science and Environmental Epidemiology*. Forthcoming.

Neelon B, Swamy GK, Burgette LF, Miranda ML. 2011. "A Bayesian Growth Mixture Model to Examine Maternal Hypertension and Birth Outcomes." *Stat.Med*. 30(22):2721-35.

Schwartz S, Li F, Reiter JP. 2012. “Sensitivity Analysis for Unmeasured Confounding in Principal Stratification Settings with Binary Variables.” *Stat.Med*. 10;31(10):949-62.

Stapleton HM, Eagle S, Anthopolos R, Wolkin A, Miranda ML. 2011. “Associations between Polybrominated Diphenyl Ether (PBDE) Flame Retardants, Phenolic Metabolites, and Thyroid Hormones during Pregnancy.” *Environ.Health Perspect*. 119(10):1454-9.

Swamy GK, Edwards S, Gelfand A, James SA, Miranda ML. 2012. “Maternal Age, Birth Order, and Race: Differential Effects on Birthweight.” *J.Epidemiol.Community Health.* 66(2):136-42.

Swamy GK, Garrett ME, Miranda ML, Ashley-Koch AE. 2011. “Maternal Vitamin D Receptor Genetic Variation Contributes to Infant Birthweight among Black Mothers*.” Am.J.Med.Genet.A*. 155A(6):1264-71.

Zhu B, Dunson D, Ashley-Koch AE. 2012. “Adverse Sub-population Regression for Multivariate Outcomes with High-dimensional Predictors.” *Stat.Med*.

Supplemental Keywords
Pregnancy, preterm birth, low birth weight, racial disparity, African American, environmental stressors, gene-environment interactions, psychosocial stressors, genes, single nucleotide polymorphisms, genetic admixture

Research Project C: Perinatal Environmental Exposure Disparity and Neonatal Respiratory Health

Period covered by the report: 5/1/2011 – 4/30/2012
EPA Agreement Number: RD83329301-0
Investigators: Richard L. Auten (PI), W. Michael Foster
Project Period: Year 5

Objectives of Research: Specific Aims

1. To determine whether maternal exposure to airborne particulates (PM) and/or ozone (1st hit) restricts fetal growth and/or postnatal growth, and impairs lung development/function in newborn mice;
2. To determine whether PM and/or ozone exposure ‘re-programs’ maternal inflammatory responses;
3. To determine whether postnatal (2nd hit) ozone exposure further impairs postnatal somatic and lung development/function following maternal PM and/or ozone exposures;
4. To determine whether genetic or developmental susceptibility to airway hyperreactivity exacerbates maternal and/or postnatal exposure effects on postnatal somatic and lung development/function.

Summary of Accomplishments

1. For Aim 4, we have distinguished the fetal versus maternal immune responses required for effects of maternal diesel exhaust (or diesel particle instillation) exposure on the induction of fetal pro-inflammatory cytokines in fetal lung, brain, and in placenta.

2. Our studies on the neural contribution of persistent airway hyperreactivity in newborn mice exposed to environmentally relevant concentrations of ozone have shown that the muscarinic receptor pathway is unaffected, and that the effects are likely relevant to alterations in airway epithelial integrity, since the ozone effects on airway mechanics are apparent with inhaled methacholine challenge, but not apparent with intravenous acetylcholine challenge. The persistence of the epithelial impairment into adulthood well beyond recovery from the intermittent sub-chronic neonatal/juvenile exposures is highly relevant to the potential contribution to susceptibility in adults, which we are now evaluating. We are also examining the afferent neural plasticity in ozone exposed newborns as a potential contributor in collaboration with Dr. David Jacoby at Oregon Health Sciences University. This work has been submitted for publication.
3. We have tested the contribution of fetal inflammation provoked by maternal diesel inhalation to susceptibility to obesity in adult mice. Diesel exposure of pregnant dams produced obese male offspring reared on a normal diet. If mice were given a high-fat diet, mice born to diesel -exposed dams had more obesity, insulin resistance, and males had higher evidence of anxiety (see manuscripts below).

Future Activities

1. Delineation of the epigenetic mechanisms that underlie the inter-generational burden of perinatal exposure to atmospheric pollutants on juvenile and adult health, in the context of post-natal co-exposures to adverse diet, air pollutants, inflammatory challenges.

2. Identification of the mechanisms of interaction between co-exposure agents during perinatal life that affect respiratory and cognitive development during juvenile development.

3. Identify the mechanism underlying the long-term impairment of airway epithelial integrity that follows perinatal and neonatal air pollutant exposures.

Publications

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Bolton JL, Smith SH, Huff NC, Gilmour MI, Foster WM, Auten RL, Bilbo SD. “Perinatal Air Pollution Exposure Induces Neuroinflammation and Predisposes Offspring to Weight Gain in Adulthood in a Sex-specific Manner.” FASEB J. In press.

Miranda ML, Edwards SE, Chang HH, Auten RL. “Proximity to Roadways and Pregnancy Outcomes.” *J. Exp Science Env Epi*. In press.

Supplemental Keywords neuroinflammation,